(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 445 811 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication of patent specification: **14.06.95**

(51) Int. Cl.[6]: **C07D 213/80**, C07D 401/10, C07D 239/36, C07D 403/10, A61K 31/455

(21) Application number: **91103497.3**

(22) Date of filing: **07.03.91**

(54) Nitrogen-containing heterocyclic compounds, their production and use.

(30) Priority: **07.03.90 JP 56205/90**
07.03.90 JP 56206/90
20.03.90 JP 71051/90

(43) Date of publication of application:
11.09.91 Bulletin 91/37

(45) Publication of the grant of the patent:
14.06.95 Bulletin 95/24

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(56) References cited:
EP-A- 0 323 841
EP-A- 0 407 342
EP-A- 0 411 766
EP-A- 0 419 048

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EP 0 445 811 B1

Description

FIELD OF THE INVENTION

The present invention relates to novel nitrogen-containing heterocyclic compounds having potent pharmacological activity and intermediates for the preparation thereof. More particularly, the present invention relates to compounds having potent anti-hypertensive activity and angiotensin II antagonist activity, which are useful as therapeutic agents for treating circulatory diseases such as hypertensive diseases, heart diseases, strokes, etc.

BACKGROUND OF THE INVENTION

The renin-angiotensin system is involved in the homeostatic function to control systemic blood pressure, the volume of body fluid, balance among the electrolytes, etc., associated with the aldosterone system. Development of angiotensin II converting enzyme inhibitors (ACE inhibitor) (this converting enzyme produces angiotensin II which possesses strong vasoconstrictive activity) has clarified the relation between the renin-angiotensin system and hypertension. Since angiotensin II elevates blood pressure via the angiotensin II receptors on cell membranes, angiotensin II antagonists as well as the ACE inhibitor would be useful in treating hypertension.

It has been reported that various angiotensin II analogues such as saralasin, [Sar^1, Ile^8]A II, and the like, possess potent angiotensin II antagonist activity.

It has, however, been reported that, when peptide antagonists are administered parenterally, their actions are not prolonged and, when administered orally, they are ineffective (M. A. Ondetti and D. W. Cushman, Annual Reports in Medicinal Chemistry, 13, 82-91 (1978)).

Non-peptide angiotensin II antagonists are disclosed in Japanese Patent Laid Open No. 71073/1981; No. 71074/1981; No. 92270/1982; No. 157768/1983; No. 240683/1987; No. 23868/1988; and No. 117876/1989, and European Patent Laid Open No. 0323841, etc.

Imidazole derivatives having angiotensin II antagonist activity are disclosed in A. T. Chiu et al., Eur. J. Pharm., 157, 13 (1981), P. C. Wong et al., J. Pharmcol. Exp. Ther., 247, 1 (1988), P. C. Wong et al., Hypertension, 13, 489 (1989), etc.

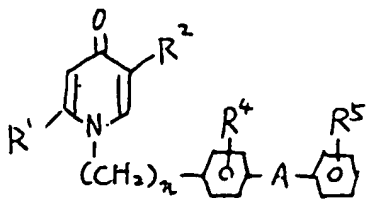
The intermediate application (i.e. falling under the terms of Art. 54(3) EPC) EP-A-0 407 342 discloses the use of pyrimidine derivatives for pharmaceutical products. The use as angiotensin II antagonists is disclosed for substituted pyrimidinones in EP-A-0 419 048 (intermediate application) and for substituted quinazolinones in EP-A-0 411 766 (intermediate application) as well as in EP-A-0 323 841 for substituted pyrroles, pyrazoles and triazoles. These four applications have the use of derivatives of six or five membered hetrocycles containing at least two nitrogens in common.

It has not yet been known that heterocyclic compounds having a nitrogen-containing 6-membered ring such as pyridone possess potent angiotensin II antagonist activity.

SUMMARY OF THE INVENTION

The present inventors made extensive investigations to prepare useful compounds which have angiotensin II antagonist activity. As a result of this research, the present inventors have succeeded in synthesizing nitrogen-containing heterocyclic compounds possessing highly potent angiotensin II antagonist activity and developed the present invention.

The present invention provides nitrogen-containing heterocyclic compounds having the formula I:



wherein R^1, optionally bound through a nitrogen, oxygen or sulfur atom, is alkyl of 1 to 8 carbon atoms, alkenyl of 2 to 8 carbon atoms, alkynyl of 2 to 8 carbon atoms, alicyclic hydrocarbon residue of 3 to 8

carbon atoms or aromatic hydrocarbon residue of 6 to 12 carbon atoms which may be substituted with hydroxyl, (C_{1-4}) alkoxy, (C_{1-4}) alkyl, halogen, nitro, amino, N-(C_{1-4}) alkylamino, N,N-di(C_{1-4}) alkylamino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino, piperidylmethyl, N-phenylpiperazino, N-(p-fluorophenyl)piperazino, N-(m-methoxyphenyl)piperazino, (C_{1-4}) alkanoyloxy, benzoyloxy, phenyl optionally substituted with halogen, nitro, (C_{1-4}) alkoxy or (C_{1-4}) alkyl, or naphthyl optionally substituted with halogen, nitro, (C_{1-4}) alkoxy or (C_{1-4}) alkyl, or R^1 is 5-methyl-2-thienyl;
R^2 is -COD wherein D is (C_{1-4}) alkoxy, hydroxy, halogen, amino, N-(C_{1-4}) alkylamino, N,N-di(C_{1-4}) alkylamino, anilino, N-methylanilino, benzylamino, phenethylamino, naphthylmethylamino, pyridylamino, pyridylmethylamino, morpholino, piperidino, piperazino, piperidylmethyl, N-phenylpiperazino or N-(p-fluorophenyl)piperazino;
R^4 is hydrogen, halogen or nitro;
R^5 is carboxyl, (C_{1-4}) alkoxycarbonyl, cyano, tetrazolyl, trifluoromethanesulfonic amide, phosphoric acid or sulfonic acid;
A is a direct bond, (C_{1-4}) alkylene, -(CO)-, -O-, -S-, -(NH)-, -(CO)-(NH)-, -O-CH_2-, -S-CH_2- or -CH=CH-;
n is an integer of 1 or 2;
or a pharmaceutically acceptable salt thereof.

These compounds are potent angiotensin II antagonists which are of value in the treatment of circulatory system diseases such as hypertensive diseases, heart diseases, strokes, etc.

Another aspect of the present invention relates to pharmaceutical compositions comprising an effective amount of the nitrogen-containing heterocyclic compound having the formula I and a pharmaceutically acceptable carrier useful in treating circulatory system diseases such as hypertensive diseases, heart diseases, strokes, etc., and processes for preparing such compounds and compositions.

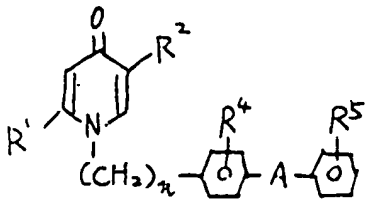
Still another aspect of the present invention relates to a method for treating said circulatory system diseases of patients, which comprises administering an effective amount of the nitrogen-containing heterocyclic compound having the formula I or the pharmaceutical composition thereof to the patient.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides nitrogen-containing heterocyclic compounds having the formula I and the pharmaceutically acceptable salts thereof, which possess potent angiotensin II antagonist activity and are of value in the treatment of circulatory diseases such as hypertensive disease, heart diseases, strokes, etc., pharmaceutical compositions comprising an effective amount of the nitrogen-containing heterocyclic compound having the formula I and a pharmaceutically acceptable carrier useful in treating said circulatory diseases and processes for preparing such compounds and compositions.

The present invention further provides a method for treating said circulatory system diseases of patients, which comprises administering an effective amount of the nitrogen containing heterocyclic compound having the formula I or the pharmaceutical composition thereof to the patient.

An important group of compounds according to the present invention are the compounds of the formula I:



wherein R^1, optionally bound through a nitrogen, oxygen or sulfur atom, is alkyl of 1 to 8 carbon atoms, alkenyl of 2 to 8 carbon atoms, alkynyl of 2 to 8 carbon atoms, alicyclic hydrocarbon residue of 3 to 8 carbon atoms or aromatic hydrocarbon residue of 6 to 12 carbon atoms which may be substituted with hydroxyl, (C_{1-4}) alkoxy, (C_{1-4}) alkyl, halogen, nitro, amino, N- (C_{1-4}) alkylamino, N,N-di(C_{1-4}) alkylamino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino morpholino, piperidino, piperazino, piperidylmethyl, N-phenylpiperazino, N-(p-fluorophenyl)piperazino, N-(m-methoxyphenyl)piperazino, (C_{1-4}) alkanoyloxy, benzoyloxy, phenyl optionally substituted with halogen, nitro, (C_{1-4}) alkoxy or (C_{1-4}) alkyl, or naphthyl optionally substituted with halogen, nitro, (C_{1-4}) alkoxy or (C_{1-4}) alkyl, or R^1 is 5-methyl-2-thienyl;
R^2 is -COD wherein D is (C_{1-4}) alkoxy, hydroxy, halogen, amino, N-(C_{1-4}) alkylamino, N,N-di(C_{1-4})

alkylamino, anilino, N-methylanilino, benzylamino, phenethylamino, naphthylmethylamino, pyridylamino, pyridylmethylamino, morpholino, piperidino, piperazino piperidylmethyl, N-phenylpiperazino or N-(p-fluorophenyl)piperazino;

R^4 is hydrogen, halogen or nitro;

R^5 is carboxyl, (C_{1-4}) alkoxycarbonyl, cyano, tetrazolyl, trifluoromethanesulfonic amide, phosphoric acid or sulfonic acid;

A is a direct bond, (C_{1-4}) alkylene, -(CO)-, -O-, -S-, -(NH)-, -(CO)-(NH)-, -O-CH_2, -S-CH_2- or -CH=CH-;

n is an integer of 1 or 2;

or a pharmaceutically acceptable salt thereof.

With regard to the foregoing formula (I), hydrocarbon residues for R^1, which may be optionally bound through a nitrogen, oxygen, or sulfur atom, are alkyls of 1 to 8 carbon atoms (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, i-pentyl, hexyl, heptyl, octyl, and the like), alkenyls of 2 to 8 carbon atoms (e.g. vinyl, allyl, isopropenyl, 2-butenyl, 1,3-butadienyl, 2-pentenyl, 2-hexenyl, 2-octenyl, and the like), and alkynyls of 2 to 8 carbon atoms (e.g. ethynyl, 2-propynyl, 2-butynyl, 2-pentynyl, 2-octynyl, and the like); alicyclic hydrocarbon residues of 3 to 8 carbon atoms (e.g. cyclopropyl, cyclopentyl, cyclohexyl, 2-cyclohexen-1-yl, cyclooctyl and the like), aromatic hydrocarbon residues of 6 to 12 carbon atoms (e.g. phenyl, naphthyl and the like); etc.

Said hydrocarbon residues for R^1 may be substituted with hydroxyl, (C_{1-4}) alkoxy (e.g. methoxy, ethoxy, and the like), (C_{1-4}) alkyl (e.g. methyl, ethyl, and the like), halogen (e.g. F, Cl, Br and the like), nitro, amino, N-(C_{1-4}) alkylamino (e.g. methylamino, ethylamino, etc.), N,N-di(C_{1-4}) alkylamino (e.g. dimethylamino, diethylamino, etc.), phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino, piperidylmethyl, N-phenylpiperazino, N-(p-fluorophenyl)piperazino, N-(m-methoxyphenyl)piperazino, (C_{1-4}) alkanoyloxy (e.g. acetyloxy, etc.) and benzoyloxy, phenyl optionally substituted with halogen, nitro, (C_{1-4}) alkoxy or (C_{1-4}) alkyl or naphthyl optionally substituted with halogen, nitro, (C_{1-4}) alkoxy or (C_{1-4}) alkyl, or R^1 is 5-methyl-2-thienyl.

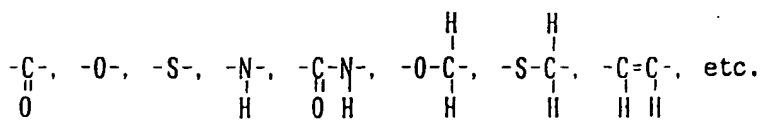
Where R^2 is a group having the formula: -COD, D is (C_{1-4}) alkoxy (e.g. methoxy, ethoxy, and the like) and hydroxy. For D, examples of halogen include Cl, Br and the like, and D is amino, N-(C_{1-4}) alkylamino (e.g. methylamino, ethylamino, propylamino, and the like), N,N-di(C_{1-4}) alkylamino (e.g. dimethylamino, diethylamino, and the like), anilino, N-methylanilino, benzylamino, phenethylamino, naphthylmethylamino, pyridylamino, pyridylmethylamino, morpholino, piperidino, piperazino, piperidylmethyl, N-phenylpiperazino or N-(p-fluorophenyl)piperazino.

The compounds wherein D is halogen are useful as synthetic intermediates for the preparation of those wherein D is alkoxy or optionally substituted amino.

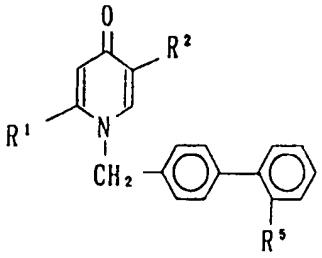
R^4 represents hydrogen, halogen (e.g. chlorine, bromine, and the like) or nitro, and may be in the ortho or meta position to the -A- group. Among them, hydrogen is most preferable.

Examples of residues capable of forming an an ion and residues convertible into the anion for R^5 include carboxyl, (C_{1-4}) alkoxycarbonyl, cyano, tetrazolyl, trifluoromethanesulfonic amide (-$NHSO_2CF_3$), phosphoric acid, sulfonic acid, and the like. Such residues may include those which are capable of forming anions or convertible into anions either chemically or under biological and/or physiological conditions. R^5 is in any positions on the phenyl group. Among them, carboxyl and tetrazolyl are preferred. R^5 is preferably in the ortho position. The compounds wherein R^5 is a residue capable of forming an anion or convertible thereinto chemically (e.g. by oxidation, reduction or hydrolysis) (e.g. cyano and the like), are useful as synthetic intermediates.

A shows that the adjacent phenylene group is bonded to the phenyl group directly or through a spacer whose atomic chain is 2 or less. As the spacer, any one can be exemplified, so long as it is a divalent chain in which the number of atoms constituting the straight chain is 1 or 2, and it may have a side chain. Examples of such spacers include (C_{1-4}) alkylene,



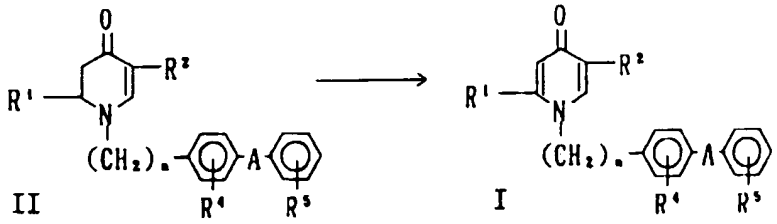
A preferred embodiment of the invention is a compound of the formula (I):



wherein R^1 is (C_{1-8}) alkyl; R^2 is -COD wherein D is hydrogen, (C_{1-4}) alkoxy, hydroxy, or optionally substituted amino (inter alia (C_{1-4}) alkyl); and R^5 is carboxyl or tetrazolyl (inter alia tetrazolyl); and the pharmaceutically acceptable salts thereof.

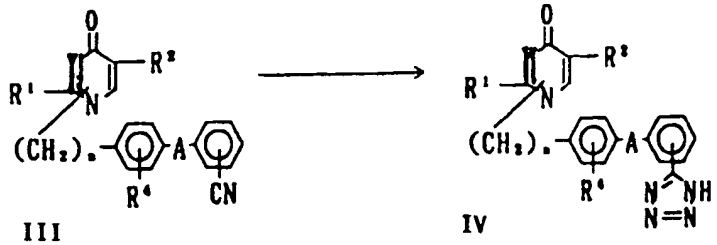
The compounds (I) of the present invention may be prepared by several reaction schemes, as illustrated below for a preferred compound.

Scheme A



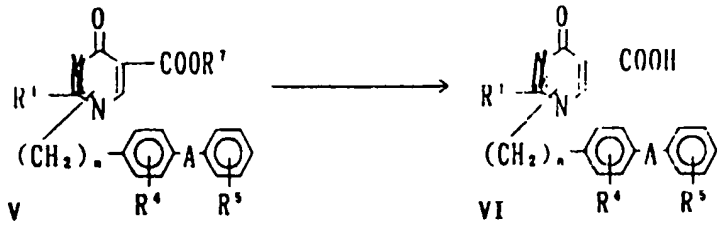
wherein R^1, R^2, R^4, R^5, A and n have the above-defined meanings.

Scheme B



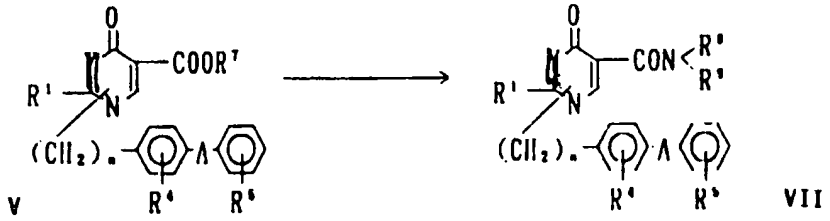
wherein R^1, R^2, R^4, A, n are as defined above.

Scheme C



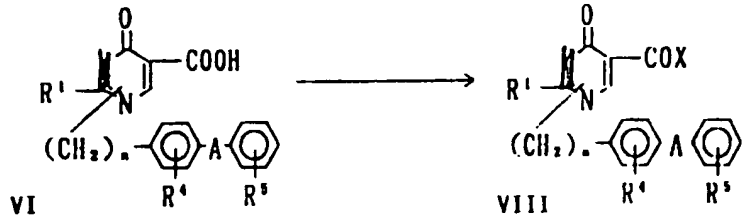
wherein R^1, R^4, R^5, A, n are as defined above and R^7 is (C_{1-4}) alkyl.

Scheme D



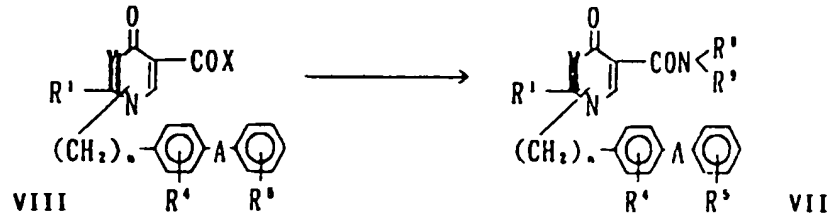
wherein R^1, R^4, R^5, R^7, A, n are as defined above and R^8 and R^9 are each independently hydrogen or a hydrocarbon residue (e.g. (C_{1-4}) alkyl and optionally substituted aryl).

Scheme E



wherein R^1, R^4, R^5, A, n are as defined above and X is halogen.

Scheme F



wherein R^1, R^4, R^5, R^8, R^9, X, A, n are as defined above.

In Scheme A, the compound (II) is reacted with an oxidizing agent to form the compound (I). One molar portion of the compound (II) is employed with approximately 1 to 3 moles of the oxidizing agent. The reaction is conventionally conducted in solvents such as benzene, toluene, tetrahydrofuran and dioxane. Examples of such oxidizing agents include 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), chloranil, and the like. Advantageously, the reaction is carried out at room temperature - 100 °C for 5 minutes - 3 hours.

The cyano substituent on the benzene of the compounds (III) is reacted with various azides to form the tetrazole compounds (IV) as illustrated in Scheme B. One molar portion of the compound (III) is employed with 1 - 10 moles of the azide. The reaction is conventionally conducted in solvents such as dimethylformamide, dimethylacetamide, toluene, benzene, and the like.

Examples of such azides include trialkyl-tin azide, triphenyl-tin azide, hydrogen azide, and the like. In the case where the organo-tin azide compound is employed, the reaction is carried out in toluene or benzene by heating under reflux for a period of from 10 - 30 hours. When the hydrogen azide is used, 5 moles of sodium azide and ammonium chloride per compound (III) are employed and the reaction is conducted in dimethylformamide at 100 °C - 130 °C for 1 - 10 days. During this reaction, it is preferable to facilitate working by adding an appropriate amount of sodium azide and ammonium chloride.

The reaction as illustrated in Scheme C is hydrolysis of the ester (V) into the carboxylic acid (VI) in the presence of an alkali. One molar portion of the compound (V) is employed with 1 to 3 moles of the alkali. The reaction is conventionally conducted in solvents such as alcohols containing water (e.g. methanol, ethanol, methylcellosolve, and the like). Examples of such alkalis include sodium hydroxide, potassium hydroxide, and the like. The reaction is preferably conducted at room temperature - 100 °C for 1 - 10 hours.

The compounds (V) are reacted with various amines to form the amide compounds (VII) as illustrated in Scheme D. One molar portion of the compound (V) is employed with about 2 to 50 moles of the amine. The reaction is conventionally conducted in solvents such as alcohols (e.g. methanol, ethanol, and the like) or without a solvent. The reaction is preferably conducted at a temperature in the range from room temperature to 200 °C. Examples of such amines include ammonia, alkylamines (e.g. methylamine, ethylamine, propylamine, dimethylamine, diethylamine, butylamine, hydroxyethylamine, etc.), aralkylamines (e.g. benzylamine, phenetylamine, N-benzyl-N-methylamine, o-methoxy-benzylamine, etc.), arylamines (e.g. aniline, N-methylaniline, etc.), heteroaralkylamines (e.g. 2-, 3- or 4-pyridylmethylamine, etc.), alicyclic amines (e.g. morpholine, piperidine, piperazine, N-phenylpiperazine, 2-piperidylmethylamine, 3-(p-fluorophenylpiperazino)propylamine, etc.), and the like.

The compounds (VI) are treated with various halogenating agents to form the acid halides (VIII) as illustrated in Scheme E. One molar portion of the compound (VI) is employed with about 1 to 5 moles of the halogenating agent. The reaction is conventionally conducted in solvents such as halogenated hydrocarbons (e.g. $CHCl_3$, CH_2Cl_2, $ClCH_2CH_2Cl$, and the like), ethers (e.g. tetrahydrofuran, dioxane, and the like) and aromatic hydrocarbons (e.g. benzene, toluene, and the like). Examples of such halogenating agents include oxalyl chloride, thionyl chloride, phosphorous oxychloride, phosphorous trichloride, phosphorous pentachloride, etc. The reaction is preferably conducted at room temperature - 100 °C for 1 - 10 hours.

The acid halides (VIII) are reacted with various amines to form the amide compounds (VII) as illustrated in Scheme F. One molar portion of the compound (VIII) is employed with about 2 to 50 moles of the amine. The reaction is conventionally conducted in solvents such as alcohols (e.g. methanol, ethanol, and the like) and ethers (e.g. ethyl ether, tetrahydrofuran, dioxane, and the like). Examples of such amines include ammonia, alkylamines (e.g. methylamine, ethylamine, propylamine, dimethylamine, diethylamine, butylamine, hydroxyethylamine, etc.), aralkylamines (e.g. benzylamine, phenethylamine, N-benzyl-N-methylamine, o-methoxybenzylamine, etc.), arylamines (e.g. aniline, N-methylaniline, etc.), heteroaralkylamines (e.g. 2-, 3- or 4-pyridylmethylamine, etc.), alicyclic amines (e.g. morpholine, piperidine, piperazine, N-phenylpiperazine, 2-piperidylmethylamine, 3-(p-fluorophenylpiperazino)propylamine, etc.), and the like.

The compounds (I) thus produced via the reaction processes as depicted in Schemes A to F can be isolated and purified from the reaction mixture according to conventional methods such as, for example, evaporation of solvents, extraction by water or organic solvents, concentration, neutralization, recrystallization, distillation, column chromatography and the like, to obtain a crystalline or oily product.

The compounds (I) of the present invention can be used in the form of salts derived from pharmaceutically or physiologically acceptable acids or bases. These salts include but are not limited to the following: salts with inorganic acids such as hydrochloric acid, sulphuric acid, nitric acid, phosphoric acid and, as the case may be, such organic acids as acetic acid, oxalic acid, succinic acid, and maleic acid. Other salts include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases.

The starting materials (II) can be easily prepared by or according to the known techniques, for example, as disclosed in:

(1) H. Narita, Y. Konishi, J. Nitta, H. Nagaki, I. Kitayama, Y. Watanabe, and I. Saikawa, Yakugaku Zasshi, 106, 775 (1986),

(2) H. Narita, Y. Konishi, J. Nitta, Y. Kobayashi, Y Watanabe, S. Minami, and I. Saikawa, Yakugaku Zasshi, 106, 787 (1986),

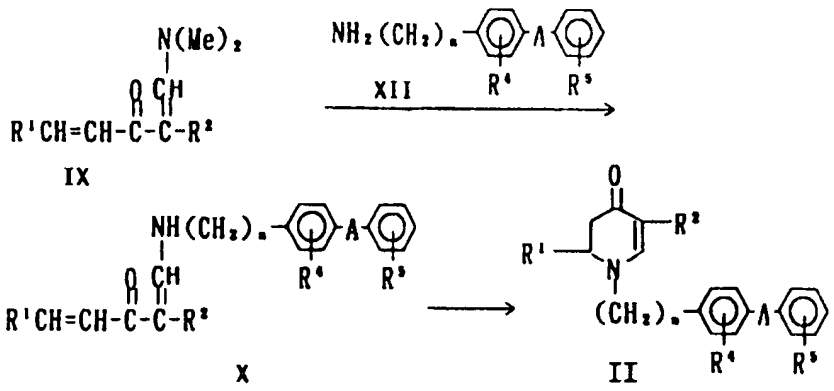
(3) Japanese Patent Laid Open No. 100382/1979,

(4) Japanese Patent Laid Open No. 157567/1979,

(5) E. E. Kilbourn, and M. C. Seidel, J. Org. Chem., 37, 1145 (1972), etc.

For example, the starting materials (II) are prepared according to the methods as illustrated in Scheme G.

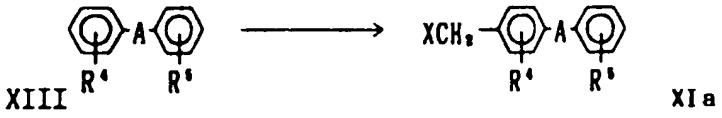
Scheme G



wherein each group is as defined above.

As illustrated in Scheme H, the compounds (XI) can also be easily prepared by halogenomethylation of the compounds (XIII) commercially available or easily prepared according to methods described in known references such as, for example, A. A. Vansheidt et al., Khim. Nauka i Prom., 2, 799 (1957).

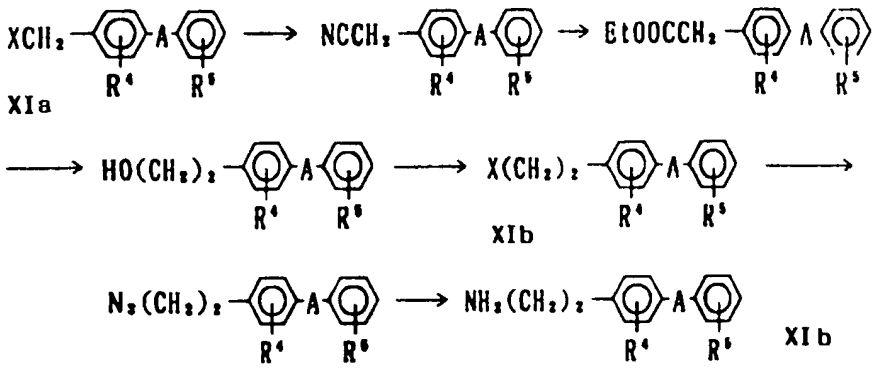
Scheme H



wherein each group has the above-defined meaning.

The compound (XII) wherein n is 2 (the compounds (XIb)) can be prepared from the compounds (XIa) according to the methods as illustrated in Scheme I.

Scheme I



wherein each group is as defined above and X is halogen.

The compounds (I) and salts thereof according to the present invention strongly inhibit vasoconstriction and hypertension derived by angiotensin II and therefore possess potent anti-hypertensive activity in animals, more specifically mammal animals (e.g. humans, dogs, rabbits, rats, etc.). Further, the compounds (I) and salts thereof according to the present invention are of quite low toxicity and useful in treating not only hypertension but also circulatory system diseases such as heart diseases, strokes and the like.

For therapeutic use, the compounds (I) and salts thereof can be administered as pharmaceutical compositions (e,g, powders, granules, tablets, pills, capsules, injections, solutions and the like) comprising at least one such compound alone or in admixture with pharmaceutically acceptable carriers, excipients and/or diluents. The pharmaceutical compositions can be formulated in accordance with conventional methods.

Specific dose levels for any particular patient will be employed depending upon a variety of factors including the activity of specific compounds employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy. When used for treating adult essential hypertension, the active ingredient will preferably be administered in an appropriate amount, for example, about 10 mg to 100 mg a day orally and about 5 mg to 50 mg a day intravenously. The active ingredient will preferably be administered in equal doses two or three times a day.

Examples

The invention is further illustrated but in no way limited by the following reference examples, working examples, pharmaceutical examples and experimental examples.

In the specification of the present application, examples of the abbreviations used are given below. Me: Methyl, Et: Ethyl, Pr: Propyl, Bu: Butyl, iBu: Isobutyl, tBu: Tert-butyl, Ac: Acetyl, Bzo: Benzoyl, Trityl: Triphenylmethyl, Ph: Phenyl, DMF: Dimethylformamide, THF: Tetrahydrofran.

Reference Example 1

A: Ethyl 3-oxo-4-nonenate

To a solution of (3-ethoxycarbonyl-2-oxopropylidene)triphenylphosphorane (5.0 g, 12.8 mmol) in tetrahydrofuran (THF, 50 ml) were added sodium hydride (60 % dispersion in oil, 1.03 g, 25.6 mmol) and then pentanal (1.10 g, 12.8 mmol) followed by stirring. After addition of water (three drops), the mixture was heated at 45 °C for 1 hour. The reaction mixture was treated with dilute hydrochloric acid and extracted with ether. The organic layer was washed with aqueous saturated sodium bicarbonate and aqueous saturated sodium chloride, dried ($MgSO_4$), and concentrated to dryness. The resulting residue was purified by column chromatography on silica gel. The column was eluted with dichloromethane-hexane (1:1 to 3:2) to give 1.02 g (40.0 %) of the title compound as an oil. The ^{1}H-NMR spectrum indicates that the product is a mixture of keto/enol isomers.

IR (neat): 2960, 1742, 1695, 1655, 1590 cm $^{-1}$.

^{1}H-NMR ($CDCl_3$) δ : 0.87-0.94(3H, m, $(CH_2)_3\underline{CH_3}$), 1.25-1.46(7H, m, $CH_2\underline{(CH_2)_2}CH_3$, $CO_2CH_2\underline{CH_3}$), 2.53-2.69(2H, m, $\underline{CH_2}(CH_2)_2CH_3$), 3.49(2H×7/13, s, $\underline{CH_2}CO_2Et$), 4.20(2H, q, J=7.2Hz, $CO_2\underline{CH_2}CH_3$), 5.00-(1H×6/13, s, $\underline{C(OH)}=\underline{CH}CO_2Et$), 5.62-5.97, 6.14-6.23(2H, m, olefin-H), 12.1(1H×6/13, d, J=1.6Hz, $\underline{C(OH)}$-$=CHCO_2Et$).

B: Ethyl 2-[(2'-t-butoxycarbonylbiphenyl-4-yl)methylaminomethylene]-3-oxo-4-nonenate

A solution of ethyl 3-oxo-4-nonenate (1.00 g, 5.04 mmol) and N,N-dimethylformamide dimethyl acetal (0.94 ml, 7.08 mmol) in benzene (10 ml) was stirred at 70°C for 1.5 hours under nitrogen stream. After cooling, a solution of 4-aminomethyl-2'-t-butoxycarbonylbiphenyl (2.86 g, ca. 10.1 mmol) in tetrahydrofuran (15 ml) was added to the reaction solution and the solution was stirred at room temperature for 2 hours and then concentrated to dryness. The resulting residue was purified by column chromatography on silica gel. The column was eluted with dichloromethane-ethyl acetate (1% to 5%) to give 1.65 g (66.6 %) of the title compound as an oil.

IR (neat): 2980, 2940, 1709, 1608 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ : 0.87-0.94(3H, m, $(CH_2)_3\underline{CH_3}$), 1.27(9H, s, $CO_2\underline{C(CH_3)_3}$), 1.27-1.51(7H, m, $CO_2CH_2\underline{CH_3}$, $CH_2\underline{(CH_2)_2}CH_3$), 2.18-2.30, 2.49-2.61(2H, m, $\underline{CH_2}(CH_2)_2CH_3$), 4.17-4.28(2H, m, $CO_2\underline{CH_2}CH_3$), 4.57-4.61(2H, m, $\underline{CH_2}Ph$), 6.83-6.98, 7.27-7.54, 7.78-7.82(10H, m, olefin-H, ArH), 8.12-8.21 (1H, m, $C=\underline{CH}NH$), 11.63(1H, br, NH).

C: Ethyl 1-[(2'-t-butoxycarbonylbiphenyl-4-yl)methyl]-6-n-butyl-4-oxo-1,4,5,6-tetrahydronicotinate

A solution of ethyl 2-[(2'-t-butoxycarbonylbiphenyl-4-yl)methylaminomethylene]-3-oxo-4-nonenate (1.59 g, 3.23 mmol) in DMF (20 ml) and was heated under reflux for 4 hours. After cooling, the reaction solution was concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel. The column was eluted with ethyl acetate-hexane (7:3 to 8:2) to give 1.21 g (76.2 %) of the title compound as an oil.

IR (neat): 2960, 2930, 1730, 1659, 1592 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ : 0.89(3H, t, J=7.0Hz, $(CH_2)_3\underline{CH_3}$), 1.17-1.40 (4H, m, $CH_2\underline{(CH_2)_2}CH_3$), 1.28(9H, s, $CO_2\underline{C(CH_3)_3}$), 1.34 (3H, t, J=7.2Hz, $CO_2CH_2\underline{CH_3}$), 1.60-1.79(2H, m, $CH_2\underline{(CH_2)_2}CH_3$), 2.38(1H, d-d, J=2.2Hz, 16.0Hz, C_5-H), 2.66(1H, d-d, J=6.6Hz, 16.0Hz, C_5-H), 3.45-3.55(1H, m, C_6-H), 4.27(2H, d-q, J=1.2Hz, 7.2Hz, $CO_2\underline{CH_2}CH_3$), 4.53, 4.69(2H, 2d, J=15.2Hz, $\underline{CH_2}Ph$), 7.27-7.56, 7.79-7.83(8H, m, ArH), 8.28(1H, s, C_2-H).

Reference Example 2

A: Ethyl 2-[[2'-(N-methoxymethyltetrazol-5-yl)biphenyl-4-yl]methylaminomethylene-3-oxo-nonenate

A solution of ethyl 3-oxo-4-nonenate (1.40 g, 7.06 mmol) and N,N-dimethylformamide dimethyl acetal (1.32 ml, 9.94 mmol) in benzene (15 ml) was stirred at 70°C for 1.5 hours under nitrogen stream. After cooling, a solution of 5-(4'-aminomethylbiphenyl-2-yl)-N-methoxymethyltetrazole (2.72 g, ca. 9.21 mmol) in benzene (15 ml) was added to the reaction solution and the mixture was stirred at room temperature for 3 hours. After evaporation, the resulting residue was purified by flash column chromatography on silica gel. The column was eluted with dichloromethane-ethyl acetate (1% to 5%) to give 1.07 g (30.1 %) of the title compound as an oil.

IR (neat): 2970, 2935, 1738, 1680, 1640, 1600, 1557 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ : 0.91(3H, t, J=7.2Hz, $(CH_2)_3\underline{CH_3}$), 1.23-1.50 (4H,m, $CH_2\underline{(CH_2)_2}CH_3$), 1.32(3H, t, J=7.0Hz, $CO_2CH_2\underline{CH_3}$), 2. 19-2.30(2H, m, $\underline{CH_2}(CH_2)_2CH_3$), 3.32(3H, s, $CH_2O\underline{CH_3}$), 4.23(2H, q, J=7.0Hz, $CO_2\underline{CH_2}CH_3$), 4.54(2H, d, J=6.2Hz, CH_2Ar), 5.74(2H, s, $\underline{CH_2}OCH_3$), 6.79-6.95(1H, m, olefin-H), 7.20(4H, s, Ar), 7.29-7.60, 7.88-7.93(5H, m, olefin-H, ArH), 8.15(1H, d, J=13.4Hz, $C=\underline{CH}NH$), 11.58 (1H, br, NH).

B: Ethyl 6-n-butyl-1-[[2'-(N-methoxymethyltetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-1,4,5,6-tetrahydronicotinate

A solution of ethyl 2-[[2'-(N-methoxymethyltetrazol-5-yl)biphenyl-4-yl]methylaminomethylene-3-oxo-nonenate (1.06 g, 2.10 mmol) in DMF (20 ml) was heated under reflux for 4 hours. After cooling, the reaction solution was concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel. The column was eluted with ethyl acetate-hexane (8:2 to 9:1) to give 0.7 g (66.2 %) of the title

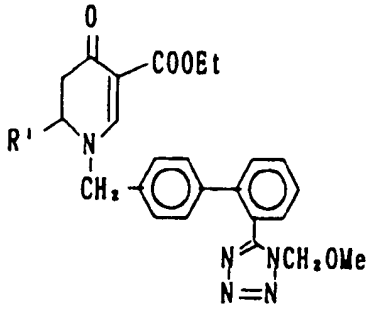
compound as a pale orange oil.

IR (neat): 2960, 2935, 1720, 1655, 1590 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ : 0.88(3H, t, J=6.8Hz, $(CH_2)_3\underline{CH_3}$), 1.21-1.37 (4H, m, $CH_2\underline{(CH_2)_2}CH_3$), 1.34(3H, t, J=7.0Hz, $CO_2CH_2\underline{CH_3}$), 1.58-1.78(2H, m, $\underline{CH_2}(CH_2)_2CH_3$), 2.39(1H, d-d, J=1.8Hz, 16.0Hz, C_5-H), 2.67(1H, d-d, J=6.4Hz, 16.0Hz, C_5-H), 3.37(3H, s, $CH_2O\underline{CH_3}$), 3.43-3.54(1H, m, C_6-H), 4.26 (2H, d-q, J=1.2Hz, 7.0Hz, $CO_2\underline{CH_2}CH_3$), 4.49, 4.63(2H, 2d, J=15.0Hz, $\underline{CH_2}Ar$), 5.75(2H, s, $\underline{CH_2}OCH_3$), 7.24-7.29, 7.44-7.63, 7.90-7.94(8H, m, ArH), 8.23 (1H, s C_2-H).

The following compounds as listed in Tables 1a and 1b were prepared according to the procedure for Reference Example 2.

TABLE 1a



Reference Example No.	R'	Appearance	IR(cm^{-1})
3	$CH_3(CH_2)_4$	pale yellow oil	(neat): 2930,1730, 1680, 1653, 1587
4	$CH_3(CH_2)_2$	pale yellow oil	(neat): 2970,1718, 1660, 1600
5	$(CH_3)_2CH(CH_2)_2$	pale orange solid	(KBr): 2950,1720, 1655, 1590
6	5-methyl-2-thienyl	pale orange solid	(KBr): 2930,1720, 1653, 1585

TABLE 1b

Reference Example No.	^{1}H-NMR ($CDCl_3$) δ
3	0.87(3H,t,J = 7.0Hz,$(CH_2)_4\underline{CH_3}$),1.20-1.40(6H,m, $CH_2\underline{(CH_2)_3CH_3}$),1.33(3H,t,J = 7.0Hz,$CO_2CH_2\underline{CH_3}$),1.59-1.79 (2H,m,$\underline{CH_2}(CH_2)_3CH_3$),2.39(1H,d-d,J = 2.0Hz,16.0Hz,C_5-H), 2.66(1H,d-d,J = 7.0Hz,16.0Hz,C_5-H),3.21(3H,s,$CH_2O\underline{CH_3}$), 3.39-3.46(1H,m,C_6-H),4.26(2H,d-q,J = 1.2Hz,7.0Hz, $CO_2\underline{CH_2}CH_3$),4.45,4.59(2H,2d,J = 15.0Hz,$\underline{CH_2}$Ar),5.17(2H,s, $\underline{CH_2}OCH_3$),7.21 (4H,s,ArH),7.55-7.61,7.66-7.75(4H,m,ArH), 8.18(1H,s,C_2-H).
4	0.90(3H,t,J = 7.0Hz,$(CH_2)_2\underline{CH_3}$),1.23-1.44(2H,m,$CH_2\underline{CH_2}CH_3$), 1.33(3H,t,J = 7.0Hz,$CO_2CH_2\underline{CH_3}$),1.52-1.75(2H,m,$\underline{CH_2}CH_2CH_3$), 2.39(1H,d-d,J = 2.0Hz,16.2Hz,C_5-H),2.66(1H,d-d,J = 7.0Hz, 16.2Hz,C_5-H),3.21(3H,s,$CH_2O\underline{CH_3}$),3.37-3.47(1H,m,C_6-H), 4.26(2H,d-q,J = 1.0Hz,7.0Hz,$CO_2\underline{CH_2}CH_3$),4.46,4.59(2H,2d, J = 15.4Hz,$\underline{CH_2}$Ar),5.17(2H,s,$\underline{CH_2}OCH_3$),7.21(4H,s,ArH), 7.55-7.61,7.66-7.73(4H,m,ArH),8.18(1H,s,C_2-H).
5	0.86(6H,d-d,J = 1.2Hz,6.6Hz,$(CH_2)_2CH\underline{(CH_3)_2}$),1.05-1.36, 1.43-1.75(5H,m,$\underline{(CH_2)_2CH}(CH_3)_2$),1.34(3H,t,J = 7.2Hz, $CO_2CH_2\underline{CH_3}$),2.39(1H,d-d,J = 2.2Hz,15.8Hz,C_5-H),2.67(1H, d-d,J = 6.8Hz,15.8Hz,C_5-H),3.37(3H,s,$CH_2O\underline{CH_3}$),3.41-3.52 (1H,m,C_6-H),4.27(2H,d-q,J = 1.8Hz,7.2Hz,$CO_2\underline{CH_2}CH_3$), 4.49,4.64(2H,2d,J = 15.2Hz,$\underline{CH_2}$Ar),5.75(2H,s,$\underline{CH_2}OCH_3$), 7.20-7.29,7.44-7.63,7.90-7.94(8H,m,ArH),8.24(1H,s,C_2-H).
6	1.34(3H,t,J = 7.2Hz,$CO_2CH_2\underline{CH_3}$),2.44(3H,d,J = 1.2Hz,$Ar\underline{CH_3}$), 2.69(1H,d-d,J = 4.0Hz,16.0Hz,C_5-H),2.94(1H,d-d,J = 7.2Hz, 16.0Hz,C_5-H),3.37(3H,s,$CH_2O\underline{CH_3}$),4.28(2H,d-q,J = 2.2Hz, 7.2Hz,$CO_2\underline{CH_2}CH_3$),4.48,4.59(2H,2d,J = 15.0Hz,$\underline{CH_2}$Ar), 4.74(1H,d-d,J = 4.0Hz,7.2Hz,C_6-H),5.74(2H,s,$\underline{CH_2}OCH_3$), 6.58(1H,d-d,J = 1.2Hz,3.4Hz,thienyl-H),6.71(1H,d,J = 3.4Hz, thienyl-H),7.19(2H,d,J = 8.6Hz,ArH),7.26(2H,d,J = 8.6Hz,ArH), 7.44-7.62,7.90-7.94(4H,m,ArH),8.29((1H,s,C_2-H).

Working Example 1

A: Ethyl 1-[(2'-t-butoxycarbonylbiphenyl-4-yl)methyl]-6-n-butyl-4-oxo-1,4-dihydronicotinate

A solution of the compound (1.39 g, 2.83 mmol) obtained in Reference Example 1C in benzene (15 ml) was heated to 80 • C under stirring and a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 0.65 g, 2.86 mmol) in benzene (36 ml) was added dropwise to the solution over 20 minutes. After heating at 80 • C for further 30 minutes, insoluble materials were removed by filtration. The filtrate was washed with dilute aqueous sodium hydroxide and aqueous saturated sodium chloride, dried ($MgSO_4$) and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel. The column was eluted with chloroform-methanol (1% to 5%) to give 0.92 g (76.0 %) of the title compound as a white crystal (recrystallization from ether-hexane).

mp: 80-81 • C.

IR (KBr): 2980, 1729, 1713, 1639, 1579 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ : 0.91(3H, t, J = 7.2Hz, $(CH_2)_3\underline{CH_3}$), 1.28(9H, s, $CO_2\underline{C(CH_3)_3}$), 1.27-1.43, 1.52-1.65-(4H, m, $CH_2\underline{(CH_2)_2}CH_3$), 1.37(3H, t, J = 7.2Hz, $CO_2CH_2\underline{CH_3}$), 2.48(2H, t, J = 8.0Hz, $\underline{CH_2}(CH_2)_2CH_3$), 4.37(2H, q, J = 7.2Hz, $CO_2\underline{CH_2}CH_3$), 5.14 (2H, s, $\underline{CH_2}Ar$), 6.46(1H, s, C_5-H), 7.07-7.11, 7.27-7.56, 7.79-7.84(8H, m, ArH), 8.24(1H, s, C_2-H).

EI-MS m/e: 489 (M^+).

Elemental Analysis for $C_{30}H_{35}NO_5$			
	C (%)	H (%)	N (%)
Calcd:	C, 73.60;	H, 7.21;	N, 2.86
Found:	C, 73.63;	H, 7.12;	N, 2.97

B: Ethyl 6-n-butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-4-oxo-1,4-dihydronicotinate

A solution of the compound (0.686 g, 1.40 mmol) obtained in Working Example 1A in a mixture of anisole (0.76 ml, 7.0 mmol) and trifluoroacetic acid (15 ml) was stirred at 0 • C for 6 hours. After evaporation in vacuo, the resulting residue was recrystallized from ether to give 0.552 g (91.0 %) of the title compound as a colorless crystal.

mp: 202-203 • C.

IR (KBr): 2960, 1729, 1702, 1635, 1544 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ : 0.85(3H, t, J = 7.2Hz, $(CH_2)_3\underline{CH_3}$), 1.23-1.59 (4H, m, $CH_2\underline{(CH_2)_2}CH_3$), 1.30(3H, t, J = 7.2Hz, $CO_2CH_2\underline{CH_3}$), 2.45(2H, t, J = 7.8Hz, $\underline{CH_2}(CH_2)_2CH_3$), 3.50(1H, br, CO_2H), 4.22(2H, q, J = 7.2Hz, $CO_2\underline{CH_2}CH_3$), 5.19(2H, s, $\underline{CH_2}AR$), 6.58(1H, s, $\underline{C_5}$-H), 7.01-7.05, 7.27-7.57, 7.92-7.96(8H, m, ArH), 8.38(1H, s, C_2-H).

Elemental Analysis for $C_{26}H_{27}NO_5$			
	C (%)	H (%)	N (%)
Calcd:	C, 72. 04;	H, 6.28;	N, 3.23
Found:	C, 71.88;	H, 6.28;	N, 3.33

Working Example 2

A: Ethyl 6-n-butyl-1-[[2'-(N-methoxymethyltetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-1,4-dihydronicotinate

A solution of the compound (0.70 g, 1.39 mmol) obtained in Reference Example 2B in benzene (10 ml) was heated to 80 • C under stirring and a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 0.316 g, 1.39 mmol) in benzene (15 ml) was added dropwise to the solution over 20 minutes. After further heating

at 80 °C for 30 minutes, insoluble materials were removed by filtration. The filtrate was washed with dilute aqueous sodium hydroxide and aqueous saturated sodium chloride, dried ($MgSO_4$) and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel. The column was eluted with chloroform-methanol (1% to 5%) to give 0.60 g (86.0 %) of the title compound as a pale yellow powder.

IR (neat): 3430, 2960, 2940, 1725, 1690, 1631, 1575 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ : 0.90(3H, t, J = 7.0Hz, $(CH_2)_3\underline{CH_3}$), 1.25-1.63 (4H, m, $CH_2\underline{(CH_2)_2}CH_3$), 1.37(3H, t, J = 7.0Hz, $CO_2CH_2\underline{CH_3}$), 2.44(2H, t, J = 7.0Hz, $\underline{CH_2}(CH_2)_2CH_3$), 3.36(3H, s, $CH_2O\underline{CH_3}$), 4.37(2H, q, J = 7.0Hz, $CO_2\underline{CH_2}CH_3$), 5.09(2H, s,$\underline{CH_2}$Ar), 5.75(2H, s, $\underline{CH_2}OCH_3$), 6.44(1H, s C_5-H).6.99(2H, d, J = 8.4Hz, ArH), 7.24-(2H, d, J = 8.4Hz, ArH), 7.41-7.59, 7.88-7.93(4H, m, ArH), 8.20(1H, s, C_2-H).

B: Ethyl 6-n-butyl-4-oxo-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]-methyl]-1,4-dihydronicotinate

A solution of the compound (0.47 g, 0.937 mmol) obtained in Working Example 2A in trifluoroacetic acid (10 ml) was stirred at 50 °C for 2.5 hours. After evaporation in vacuo, the resulting residue was purified by flash column chromatography on silica gel. The column was eluted with chloroform-methanol (1% to 5%) to give 0.193 g (45.0 %) of the title compound as a colorless crystal (recrystallization from ethyl acetate-ether).

mp: 119-120 °C.

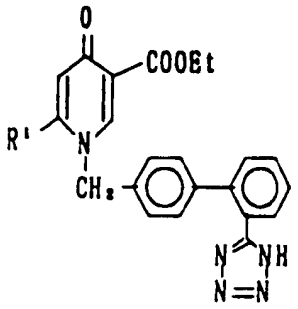
IR (KBr) : 2960, 1728, 1638, 1568 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ : 0.81(3H, t, J = 7.4Hz, $(CH_2)_3\underline{CH_3}$), 1.17-1.55 (4H, m, $CH_2\underline{(CH_2)_2}CH_3$), 1.30(3H, t, J = 7.0Hz, $CO_2CH_2\underline{CH_3}$), 2.29(2H, t, J = 7.4Hz, $\underline{CH_2}(CH_2)_2CH_3$), 4.15(2H, q, J = 7.0Hz, $CO_2\underline{CH_2}CH_3$), 5.26(2H, s, $\underline{CH_2}$Ar), 6.29(1H, s, C_5-H), 6.68(2H, d, J = 8.0Hz, ArH), 7.01 (2H, d, J = 8.0Hz, ArH), 7.35-7.39, 7.53-7.56, 7.87-7.89(4H, m, ArH), 9.04(1H, s, C_2-H).

Elemental Analysis for $C_{26}H_{27}N_5O_3 \cdot 0.1H_2O$			
	C (%)	H (%)	N (%)
Calcd:	C, 67.99;	H, 5.97;	N, 15.25
Found:	C, 67.83;	H, 5.93;	N, 15.11

The following compounds as listed in Tables 2a and 2b were prepared from the compounds obtained in Reference Examples 3-6 in the same manner as in Working Example 2.

TABLE 2a



Working Example No.	R¹	mp (°C)	IR(cm⁻¹)	E. Anal. (Calcd/Found) C(%), H(%), N(%)
3	$CH_3(CH_2)_4$	115-117	(KBr): 2960, 1725, 1690, 1635, 1557	$C_{27}H_{29}N_5O_3 \cdot 0.3H_2O$ C,67.99;H,6.26;N,14.68 C,67.88;H,6.12;N,14.45
4	$CH_3(CH_2)_2$	141-142	(KBr): 2970, 1728, 1688, 1635,1573	$C_{25}H_{25}N_5O_3 \cdot 0.2H_2O$, C,67.16;H,5.73;N,15.66 C,66.97;H,5.56;N,15.66
5	$(CH_3)_2CH(CH_2)_2$	128-129	(KBr): 2960, 1720, 1693, 1642, 1567	$C_{27}H_{29}N_5O_3$ C,68.77;H,6.20;N,14.85 C,68.70;H,6.20;N,15.03
6	5-methyl-2-thienyl	234-236	(KBr): 2980, 1732, 1630, 1552	$C_{27}H_{23}N_5O_3S$ C,65.18;H,4.66;N,14.07 C,65.31;H,4.65;N,14.16

TABLE 2b

Working Example No.	^{1}H-NMR ($CDCl_3$) δ
3	0.80(3H,t,J = 6.6Hz,$(CH_2)_4$ $\underline{CH_3}$),1.15-1.24(4H,m, $CH_2CH_2(\underline{CH_2})_2CH_3$),1.30(3H,t,J = 7.0Hz,$CO_2CH_2\underline{CH_3}$),1.45-1.52 (2H,m,$CH_2\underline{CH_2}(CH_2)_2CH_3$),2.28(2H,t,J = 7.6Hz,$\underline{CH_2}(CH_2)_3CH_3$), 4,15(2H,q,J = 7.0Hz,$CO_2\underline{CH_2}CH_3$),5.26(2H,s,$\underline{CH_2}$Ar),6.28(1H,s, C_5-H),6.67(2H,d,J = 8.4Hz,ArH),7.00(2H,d,J = 8.4Hz,ArH), 7.34-7.38,7.53-7.57,7.86-7.88(4H,m,ArH),9.04(1H,s,$\underline{C_2}$-H).
4	0.87(3H,t,J = 7.6Hz,$(CH_2)_2\underline{CH_3}$),1.30(3H,t,J = 7.0Hz, $CO_2CH_2\underline{CH_3}$),1.44-1.68(2H,m,$CH_2\underline{CH_2}CH_3$),2.27(2H,t,J = 7.6Hz, $\underline{CH_2}CH_2CH_3$),4.15(2H,q,J = 7.0Hz,$CO_2\underline{CH_2}CH_3$),5.26(2H,s, $\underline{CH_2}$Ar),6.28(1H,s,C_5-H),6.68(2H,d,J = 8.4Hz,ArH),7.01 (2H,d,J = 8.4Hz,ArH),7.35-7.39,7.53-7.58,7.86-7.90(4H,m,ArH), 9.03(1H,s,C_2-H).
5	0.78(6H,d,J = 6.2Hz,$(CH_2)_2CH(CH_3)_2$),1.30(3H,t,J = 7.0Hz, $CO_2CH_2\underline{CH_3}$),1.33-1.58(3H,m,$CH_2\underline{CH_2}CH(CH_3)_2$),2.27(2H,t, J = 7.6Hz,$\underline{CH_2}CH_2CH(CH_3)_2$),4.15(2H,q,J = 7.0Hz,$CO_2\underline{CH_2}CH_3$), 5.26(2H,s,$\underline{CH_2}$Ar),6.28(1H,s,$C_5$-H),6.68(2H,d,J = 8.4Hz,ArH), 7.01(2H,d,J = 8.4Hz,ArH),7.34-7.38,7.50-7.56,7.86-7.91(4H, m,ArH),9.04(1H,s,C_2-H).
6	1.28(3H,t,J = 7.0Hz,$CO_2CH_2\underline{CH_3}$),2.43(3H,s,Ar$\underline{CH_3}$),4.14(2H,q, J = 7.0Hz,$CO_2\underline{CH_2}CH_3$),5.23(2H,s,$\underline{CH_2}$Ar),6.47(1H,s,C_5-H), 6.52(1H,d,J = 3.6Hz,thienyl-H),6.61(1H,d-d,J = 1.0Hz,3.6Hz, thienyl-H),6.74(2H,d,J = 8.2Hz,ArH),7.06(2H,d,J = 8.2Hz,ArH), 7.40-7.62,7.84-7.88(4H,m,ArH),8.98((1H,s,C_2-H).

Experimental Example 1

Inhibition of binding of angiotensin-II to angiotensin receptor

[Method]

An experiment of inhibition on the binding of angiotensin-II (A-II) to A-II-receptor was conducted by modifying the method of Douglas et al. [Endocrinology, 102, 685-696 (1978)]. An A-II-receptor was prepared from the membrane fraction of bovine adrenal cortex.

The compound of the present invention (10^{-9}M to 3 x 10^{-5}M) and ^{125}I-A-II (1.85 kBq/50 µl) were added to the receptor membrane fraction, and the mixture was incubated at room temperature for one hour. The receptor-bound and free ^{125}I-A-II were separated through a filter (Whatman GF/B filter), and the radioactivity of ^{125}I-A-II bound to the receptor was measured.

[Results]

The results relating to the compounds of the present invention are shown in Table 3.

Experimental Example 2

Inhibitory effect of the compound of the present invention on pressor action of A-II

[Method]

Jcl : SD rats (9 week old, male) were used. On the day previous to the experiment, these animals were applied with cannulation into the femoral artery and vein under anesthesia with pentobarbital Na. The animals were fasted but allowed free access to drinking water until the experiment was started. Just on the day of conducting the experiment, the artery cannula was connected with a blood-pressure transducer, and the average blood pressure was recorded by means of polygraph. Before administration of the drug, the pressor action due to intravenous administration of A-II (100 ng/kg) as the control was measured. The drugs were orally administered, and then, at each point of the measurement, A-II was administered intravenously, and the pressor action was similarly measured. By comparing the pressor action before and after administration of the drug, the percent inhibition by the drug on A-II-induced pressor action was evaluated.

[Results]

The results relating to the compounds of the present invention are shown in Table 3.

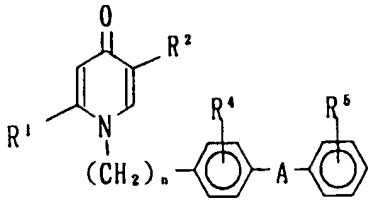
TABLE 3

Working Example	Radio Receptor 10^{-7}(M)	Assay(% Inhibition) 10^{-6}(M)	Pressor Response (30 mg/Kg, p.o.)
1	24	67	NT *a
2	25	67	NT
3	28	71	NT
4	31	72	NT

*a : NT , not tested.
*b : (% Inhibition), + ≥ 70 %.

Claims

1. A compound of the formula (I):



(I)

wherein R^1, optionally bound through a nitrogen, oxygen or sulfur atom, is alkyl of 1 to 8 carbon atoms, alkenyl of 2 to 8 carbon atoms, alkynyl of 2 to 8 carbon atoms, alicyclic hydrocarbon residue of 3 to 8 carbon atoms or aromatic hydrocarbon residue of 6 to 12 carbon atoms which may be substituted with hydroxyl, (C_{1-4}) alkoxy, (C_{1-4}) alkyl, halogen, nitro, amino, N-(C_{1-4}) alkylamino, N,N-di(C_{1-4}) alkylamino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino, piperidylmethyl, N-phenylpiperazino, N-(p-fluorophenyl)piperazino, N-(m-methoxyphenyl)-piperazino, (C_{1-4}) alkanoyloxy, benzoyloxy, phenyl optionally substituted with halogen, nitro, (C_{1-4}) alkoxy or (C_{1-4}) alkyl, or naphthyl optionally substituted with halogen, nitro, (C_{1-4}) alkoxy or (C_{1-4}) alkyl, or R^1 is 5-methyl-2-thienyl;
R^2 is -COD wherein D is (C_{1-4}) alkoxy, hydroxy, halogen, amino, N-(C_{1-4}) alkylamino, N,N-di(C_{1-4}) alkylamino, anilino, N-methylanilino, benzylamino, phenethylamino, naphthylmethylamino, pyridylamino, pyridylmethylamino, morpholino, piperidino, piperazino, piperidylmethyl, N-phenylpiperazino or N-(p-fluorophenyl)piperazino;
R^4 is hydrogen, halogen or nitro;
R^5 is carboxyl, (C_{1-4}) alkoxycarbonyl, cyano, tetrazolyl, trifluoromethanesulfonic amide, phosphoric acid or sulfonic acid;
A is a direct bond, (C_{1-4}) alkylene, -(CO)-, -O-, -S-, -(NH)-, -(CO)-(NH)-, -O-CH_2-, -S-CH_2- or -CH = CH-;
n is an integer of 1 or 2;
or a pharmaceutically acceptable salt thereof.

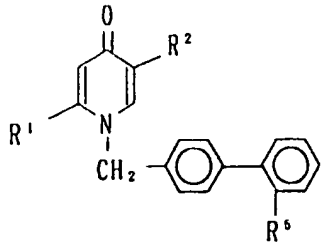
2. A compound according to claim 1, wherein R^4 is hydrogen.

3. A compound according to claim 1, wherein R^5 is carboxyl or tetrazolyl.

4. A compound according to claim 1, wherein R^5 is tetrazolyl.

5. A compound according to claim 1, wherein R^5 is in the ortho position.

6. A compound according to claim 1, which is a compound of the formula (Ia'):



wherein R^1 is (C_{1-8}) alkyl; R^2 is -COD wherein D is hydrogen, (C_{1-4}) alkoxy, hydroxy, amino, N-(C_{1-4}) alkylamino, N,N-di(C_{1-4}) alkylamino, anilino, N-methylanilino, benzylamino, phenethylamino, naphthylmethylamino, pyridylamino, pyridylmethylamino, morpholino, piperidino, piperazino, piperidylmethyl, N-

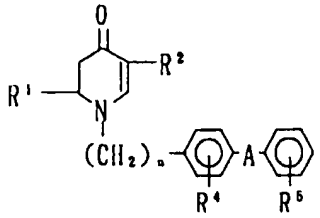
phenyl-piperazino or N-(p-fluorophenyl)piperazino; and R^5 is carboxyl or tetrazolyl; or a pharmaceutically acceptable salt thereof.

7. A compound according to claim 1 or a pharmaceutically acceptable salt thereof, which is ethyl 6-n-butyl-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-1,4-dihydronicotinate.

8. A pharmaceutical composition for antagonizing angiotensin II which comprises a therapeutically effective amount of a compound according to one of claims 1-7 or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutical acceptable carrier, excipient or diluent.

9. Use of a compound according to one of claims 1-7 of a pharmaceutically acceptable salt thereof for the manufacture of a medicament for antagonizing angiotensin II.

10. A method for producing a compound according to claim 1 which comprises oxidizing a compound of the formula (II):

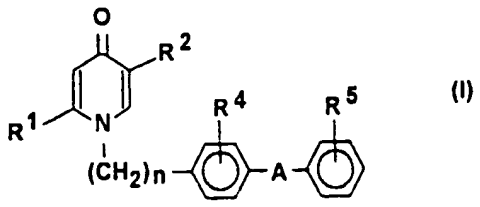


(II)

wherein R^1, R^2, R^4, R^5, A and n have the above-defined meanings, and, (i) if desired, converting a compound of the formula (I) wherein R^5 is cyano or protected tetrazolyl, and R^1, R^2, R^4, A, Y, n have the above-defined meanings, into a compound of the formula (I) wherein R^5 is tetrazolyl and R^1, R^2, R^4, A, Y, n have the above-defined meanings, (ii) if desired, converting a compound of the formula (I) wherein $-R^2$ is (C_{1-4}) alkoxycarbonyl or halogenocarbonyl, and R^1, R^4, R^5, A, Y, n have the above-defined meanings, into a compound of the formula (I) wherein $-R^2$ is carboxyl, or optionally substituted carbamoyl and R^1, R^4, R^5, A, Y, n have the above-defined meanings, (iii) if desired, converting a compound of the formula (I) wherein $-R^2$ is carboxyl, and R^1, R^4, R^5, A, Y, n have the above-defined meanings, into a compound of the formula (I) wherein $-R^2$ is halogenocarbonyl and R^1, R^4, R^5, A, Y, n have the above-defined meanings, or (iv) if desired, converting a hydroxy derivative of the formula (I) into an optionally substituted alkoxy derivative of the formula (I), and, if desired, converting a compound of the formula (I) into a pharmaceutically acceptable salt thereof.

Patentansprüche

1. Verbindung der Formel (I):



(I)

worin R^1, gegebenenfalls verbunden durch ein Stickstoff-, Sauerstoff- oder Schwefelatom, Alkyl mit 1 bis 8 Kohlenstoffatomen, Alkenyl mit 2 bis 8 Kohlenstoffatomen, Alkinyl mit 2 bis 8 Kohlenstoffatomen, einen alicyclischen Kohlenwasserstoffrest mit 3 bis 8 Kohlenstoffatomen oder einen aromatischen Kohlenwasserstoffrest mit 6 bis 12 Kohlenstoffatomen bedeutet, die mit Hydroxyl, (C_{1-4})-Alkoxy, (C_{1-4})-Alkyl, Halogen, Nitro, Amino, N-(C_{1-4})-Alkylamino, N,N-Di(C_{1-4})-alkylamino, Phenylamino,

Naphthylamino, Benzylamino, Naphthylmethylamino, Morpholino, Piperidino, Piperazino, Piperidylmethyl, N-Phenylpiperazino, N-(p-Fluorphenyl)piperazino, N-(m-Methoxyphenyl)piperazino, (C_{1-4})-Alkanoyloxy, Bemzoyloxy, Phenyl, gegebenenfalls substituiert mit Halogen, Nitro, (C_{1-4})-Alkoxy oder (C_{1-4})-Alkyl, oder Naphthyl, gegebenenfalls substituiert mit Halogen, Nitro, (C_{1-4})-Alkoxy oder (C_{1-4})-Alkyl, substituiert sein können oder R^1 5-Methyl-2-thienyl bedeutet;

R^2 -COD darstellt, worin D (C_{1-4})-Alkoxy, Hydroxy, Halogen, Amino, N-(C_{1-4})-Alkylamino, N,N-Di-(C_{1-4})-alkylamino, Anilino, N-Methylanilino, Benzylamino, Phenethylamino, Naphthylmethylamino, Pyridylamino, Pyridylmethylamino, Morpholino, Piperidino, Piperazino, Piperidylmethyl, N-Phenylpiperazino oder N-(p-Fluorphenyl)piperazino bedeutet;

R^4 Wasserstoff, Halogen oder Nitro bedeutet;

R^5 Carboxyl, (C_{1-4})-Alkoxycarbonyl, Cyano, Tetrazolyl, Trifluormethansulfonsäureamid, Phosphorsäure oder Sulfonsäure darstellt;

A eine direkte Bindung, (C_{1-4})-Alkylen, -(CO)-, -O-, -S-, -(NH)-, -(CO)-(NH)-, -O-CH_2-, -S-CH_2- oder -CH = CH- darstellt;

n eine ganze Zahl von 1 oder 2 ist;

oder ein pharmazeutisch verträgliches Salz davon.

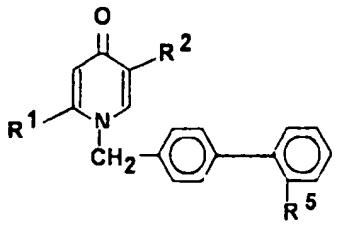
2. Verbindung nach Anspruch 1, worin R^4 Wasserstoff darstellt.

3. Verbindung nach Anspruch 1, worin R^5 Carboxyl oder Tetrazolyl darstellt.

4. Verbindung nach Anspruch 1, worin R^5 Tetrazolyl darstellt.

5. Verbindung nach Anspruch 1, worin R^5 die ortho-Stellung besetzt.

6. Verbindung nach Anspruch 1, die eine Verbindung der Formel (Ia') darstellt:



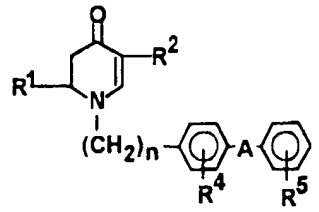
worin R^1 (C_{1-8})-Alkyl darstellt; R^2 -COD darstellt, worin D Wasserstoff, (C_{1-4})-Alkoxy, Hydroxy, Amino, N-(C_{1-4})-Alkylamino, N,N-Di-(C_{1-4})-alkylamino, Anilino, N-Methylanilino, Benzylamino, Phenethylamino, Naphthylmethylamino, Pyridylamino, Pyridylmethylamino, Morpholino, Piperidino, Piperazino, Piperidylmethyl, N-Phenylpiperazino oder N-(p-Fluorphenyl)piperazino bedeutet; und R^5 Carboxyl oder Tetrazolyl darstellt; oder ein pharmazeutisch verträgliches Salz davon.

7. Verbindung nach Anspruch 1 oder ein pharmazeutisch verträgliches Salz davon, nämlich 6-n-Butyl-1-[-[2'-(1H-tetrazolyl-5-yl)-biphenyl-4-yl]methyl]-4-oxo-1,4-dihydronicotinsäureethylester.

8. Pharmazeutische Zusammensetzung zum Entgegenwirken von Angiotensin II, umfassend eine therapeutisch wirksame Menge einer Verbindung nach einem der Ansprüche 1-7 oder ein pharmazeutisch verträgliches Salz davon in Anmischung mit einem pharmazeutisch verträglichen Träger, Exzipienten oder Verdünnungsmittel.

9. Verwendung einer Verbindung nach einem der Ansprüche 1-7 oder eines pharmazeutisch verträglichen Salzes davon zur Herstellung eines Arzneimittels zum Entgegenwirken von Angiotensin II.

10. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, umfassend Oxidieren einer Verbindung der Formel (II):



(II)

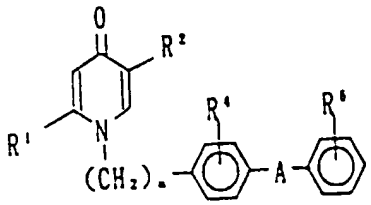
worin R^1, R^2, R^4, R^5, A und n die vorstehend definierten Bedeutungen aufweisen,

und (i) falls erwünscht, Umwandeln einer Verbindung der Formel (I), worin R^5 Cyano oder geschütztes Tetrazolyl darstellt, und R^1, R^2, R^4, A, Y, n die vorstehend definierten Bedeutungen aufweisen, in eine Verbindung der Formel (I), worin R^5 Tetrazolyl darstellt und R^1, R^2, R^4, A, Y, n die vorstehend definierten Bedeutungen aufweisen, (ii) falls erwünscht, Umwandeln einer Verbindung der Formel (I), worin $-R^2$ (C_{1-4})-Alkoxycarbonyl oder Halogencarbonyl bedeutet, und R^1, R^4, R^5, A, Y, n die vorstehend definierten Bedeutungen aufweisen, in eine Verbindung der Formel (I), worin $-R^2$ Carboxyl oder gegebenenfalls substituiertes Carbamoyl darstellt und R^1, R^4, R^5, A, Y, n die vorstehend definierten Bedeutungen aufweisen, (iii) falls erwünscht, Umwandeln einer Verbindung der Formel (I), worin $-R^2$ Carboxyl bedeutet, und R^1, R^4, R^5, A, Y, n die vorstehend definierten Bedeutungen aufweisen, in eine Verbindung der Formel (I), worin $-R^2$ Halogencarbonyl bedeutet, und R^1, R^4, R^5, A, Y, n die vorstehend definierten Bedeutungen aufweisen, oder (iv) falls erwünscht, Umwandeln eines Hydroxyderivats der Formel (I) in ein gegebenenfalls substituiertes Alkoxyderivat der Formel (I) und, falls erwünscht, Umwandeln einer Verbindung der Formel (I) in ein pharmazeutisch vertragliches Salz davon.

Revendications

1. Composé de formule (I) :

(I)



dans laquelle

R^1, éventuellement lié par l'intermédiaire d'un atome d'azote, d'oxygène ou de soufre, représente un groupe alkyle comportant de 1 à 8 atomes de carbone, un groupe alcényle comportant de 2 à 8 atomes de carbone, un groupe alcynyle comportant de 2 à 8 atomes de carbone, un résidu hydrocarboné alicyclique comportant de 3 à 8 atomes de carbone ou un résidu hydrocarboné aromatique comportant de 6 à 12 atomes de carbone qui peut être substitué par un hydroxyle, alcoxy en C_{1-4}, alkyle en C_{1-4}, halogéno, nitro, amino, N-(alkyle en C_{1-4})-amino, N,N-di-(alkyle en C_{1-4})-amino, phénylamino, naphtylamino, benzylamino, naphtylméthylamino, morpholino, pipéridino, pipérazino, pipéridinylméthyle, N-phénylpipérazino, N-(p-fluorophényl)pipérazino, N-(m-méthoxyphényl)-pipérazino, alcanoyloxy en C_{1-4}, benzoyloxy, phényle pouvant être substitué par un atome d'halogène, un groupe nitro, alcoxy en C_{1-4} ou alkyle en C_{1-4}, ou un groupe naphtyle pouvant être substitué par un atome d'halogène, un groupe nitro, alcoxy en C_{1-4} ou alkyle en C_{1-4}, ou R^1 représente un groupe 5-méthyl-2-thiényle,

R^2 représente un groupe -COD, où D représente un groupe alcoxy en C_{1-4}, hydroxy, halogéno, amino, N-(alkyle en C_{1-4})-amino, N,N-di-(alkyle en C_{1-4})-amino, anilino, N-méthylanilino, benzylamino, phénéthylamino, naphtylméthylamino, pyridylamino, pyridylméthylamino, morpholino, pipéridino, pipérazino, pipéridylméthyle, N-phénylpipérazino ou N-(p-fluorophényl)pipérazino,

R^4 représente un atome d'hydrogène, d'halogène ou un groupe nitro,

R^5 représente un groupe carboxyle, (alcoxy en C_{1-4})-carbonyle, cyano, tétrazolyle, trifluorométhanesulfonamide, acide phosphorique ou acide sulfonique,
A représente une liaison directe, un groupe alkylène en C_{1-4}, un groupe -(CO)-, -O-, -S-, -(NH)-, -(CO)-(NH)-, $-O-CH_2-$, $-S-CH_2-$ ou -CH=CH-,
n représente un nombre entier égal à 1 ou 2,
ou un sel pharmaceutiquement acceptable de celui-ci.

2. Composé conforme à la revendication 1 dans lequel R^4 représente un atome d'hydrogène.

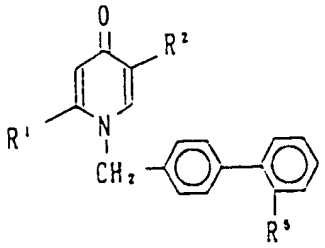
3. Composé conforme à la revendication 1 dans lequel R^5 représente un groupe carboxyle ou tétrazolyle.

4. Composé conforme à la revendication 1 dans lequel R^5 représente un groupe tétrazolyle.

5. Composé conforme à la revendication 1 dans lequel R^5 se trouve en position ortho.

6. Composé conforme à la revendication 1 qui est un composé de formule (Ia') :

(Ia')



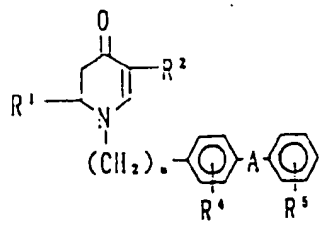
dans laquelle
R^1 représente un groupe alkyle en C_{1-8},
R^2 représente un groupe -COD où D est un atome d'hydrogène, un groupe alcoxy en C_{1-4}, hydroxy, amino, N-(alkyle en C_{1-4})-amino, N,N-di-(alkyle en C_{1-4})-amino, anilino, N-méthylanilino benzylamino phénéthylamino, naphtylméthylamino, pyridylamino, pyridylméthylamino, morpholino, pipéridino, pipérazino, pipéridylméthyle N-phénylpipérazino ou N-(p-fluorophényl)pipérazino, et
R^5 représente un groupe carboxyle ou tétrazolyle, ou un sel pharmaceutiquement acceptable d'un tel composé.

7. Composé conforme à la revendication 1 ou un sel pharmaceutiquement acceptable d'un tel composé qui est le 6-n-butyl-1-[[2'-(1H-tétrazol-5-yl)-biphényl-4-yl]méthyl]-4-oxo-1,4-dihydronicotinate d'éthyle.

8. Composition pharmaceutique à effet antagoniste de l'angiotensine II comprenant une quantité thérapeutiquement efficace d'un composé conforme à une des revendications 1 à 7 ou d'un sel pharmaceutiquement acceptable de celui-ci, mélangée à un support, excipient ou diluant pharmaceutiquement acceptable.

9. Utilisation d'un composé conforme à une des revendications 1 à 7 ou d'un sel pharmaceutiquement acceptable de celui-ci pour la préparation d'un médicament ayant un effet antagoniste de l'angiotensine II.

10. Procédé de préparation d'un composé conforme à la revendication 1, consistant à
oxyder un composé de formule (II) :

(II) 

dans laquelle R^1, R^2, R^4, R^5, A et n ont la signification définie ci-dessus, et

(i) si on le souhaite, à convertir un composé de formule (I) dans lequel R^5 est un groupe cyano ou un groupe tétrazolyle protégé et R^1, R^2, R^4, A, Y et n ont la signification donnée ci-dessus en un composé de formule (I) dans lequel R^5 est un groupe tétrazolyle et R^1, R^2, R^4, A, Y et n ont la signification donnée ci-dessus,

(ii) si on le souhaite, à convertir un composé de formule (I) dans lequel $-R^2$ est un groupe (alcoxy en C_{1-4})-carbonyle ou halogénocarbonyle et R^1, R^5, R^4, A, Y et n ont la signification donnée ci-dessus en un composé de formule (I) dans lequel $-R^2$ est un groupe carboxyle ou un groupe carbamoyle pouvant être substitué, et R^1, R^5, R^4, A, Y et n ont la signification donnée ci-dessus,

(iii) si on le souhaite, à convertir un composé de formule (I) dans lequel $-R^2$ est un groupe carboxyle et R^1, R^5, R^4, A, Y et n ont la signification donnée ci-dessus en un composé de formule (I) dans lequel $-R^2$ est un groupe halogénocarbonyle et R^1, R^5, R^4, A, Y et n ont la signification donnée ci-dessus, ou

(iv) si on le souhaite, à convertir un dérivé hydroxylé de formule (I) en un dérivé alcoxylé pouvant être substitué de formule (I), et

à convertir, si on le souhaite, un composé de formule (I) en son sel pharmaceutiquement acceptable.